PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY To: WRITTEN OPINION OF THE see form PCT/ISA/220 INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) Applicant's or agent's file reference FOR FURTHER ACTION See paragraph 2 below see form PCT/ISA/220 Priority date (day/month/year) International filing date (day/month/year) International application No. 21.10.2004 21.03.2005 PCT/GB2005/001050 International Patent Classification (IPC) or both national classification and IPC C07D243/24 Applicant ARROW THERAPEUTICS LIMITED This opinion contains indications relating to the following items: Box No. I Basis of the opinion ☐ Box No. II Priority Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. III Lack of unity of invention ☐ Box No. IV Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial ☑ Box No. V applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited Certain defects in the international application ☐ Box No. VII ☐ Box No. VIII Certain observations on the international application **FURTHER ACTION** 2. If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220. For further details, see notes to Form PCT/ISA/220. 3. **Authorized Officer** Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/GB2005/001050

	Box N	o. I Basis of the opinion	
1.	With re	gard to the language, this opinion has been established on the basis of the international application in guage in which it was filed, unless otherwise indicated under this item.	
	laı	is opinion has been established on the basis of a translation from the original language into the following inguage—, which is the language of a translation furnished for the purposes of international search index Rules 12.3 and 23.1(b)).	
2.	With renecess	With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:	
	a. type	a. type of material:	
		a sequence listing	
		table(s) related to the sequence listing	
	b. forn	nat of material:	
		in written format	
		in computer readable form	
	c. time	e of filing/furnishing:	
		contained in the international application as filed.	
		filed together with the international application in computer readable form.	
		furnished subsequently to this Authority for the purposes of search.	
3	h C	addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto as been filed or furnished, the required statements that the information in the subsequent or additional opies is identical to that in the application as filed or does not go beyond the application as filed, as ppropriate, were furnished.	
4	. Additi	onal comments:	

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

No:

Claims

1-12

Inventive step (IS)

Yes: Claims

No: Claims

Industrial applicability (IA)

Yes: Claims No: Claims 1-12

1-12

2. Citations and explanations

see separate sheet

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/GB2005/001050

- D1: SHI Y-J ET AL: "Crystallization-induced asymmetric transformation: stereospecific syntehsis of L-768,673" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, no. 4, 22 January 1999 (1999-01-22), pages 909-918, XP004151316 ISSN: 0040-4020
- D2: P. J. REIDER ET AL.: "Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of a Potent Peripheral CCK Antagonist" J ORG CHEM, vol. 52, 1987, pages 955-957, XP002330844
- D3: WO 02/30912 A (MERCK SHARP & DOHME LIMITED; CHURCHER, IAN; NADIN, ALAN, JOHN; OWENS,) 18 April 2002 (2002-04-18)
- D4: WO 95/14694 A (MERCK & CO., INC; BALDWIN, JOHN, J; CLAREMON, DAVID, A; ELLIOTT, JASON) 1 June 1995 (1995-06-01)
- D5: BUTCHER J W ET AL: "Preparation of 3-Amino-1,4-Benzodiazepin-2-Ones Via Direct Azidation with Trisyl Azide" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 37, 9 September 1996 (1996-09-09), pages 6685-6688, XP004088066 ISSN: 0040-4039
- D6: US-A-5 852 010 (GRAHAM ET AL) 22 December 1998 (1998-12-22)
- D7: WO 93/17011 A (MERCK SHARP & DOHME LIMITED) 2 September 1993 (1993-09-02)
- D8: WO 00/66106 A (THE REGENTS OF THE UNIVERSITY OF MICHIGAN; GLICK, GARY, D; OPIPARI, AN) 9 November 2000 (2000-11-09)
- D9: WO 01/90084 A (MERCK SHARP & DOHME LIMITED; CASTRO PINEIRO, JOSE, LUIS; CHURCHER, IAN) 29 November 2001 (2001-11-29)
- D10: WO 95/14471 A (MERCK & CO., INC; BALDWIN, JOHN, J; CLAREMON, DAVID, A; ELLIOTT, JASON) 1 June 1995 (1995-06-01)
- D11: WO 2004/026843 A (ARROW THERAPEUTICS LIMITED; CARTER, MALCOLM; HENDERSON, ELISA; KELSEY,) 1 April 2004 (2004-04-01)

1. Novelty

- 1.1 The subject matter of present claim 1 is not novel having regard to the disclosure of D1 and D2 and D3:
 - Documents D1 and D2 disclose crystallization induced asymmetric transformation of

a compound according to formula (II) and/or (Iia) to a compound of formula (I). Reference is made to D1: scheme 2 (protecting group: CF3-CH2-) and to D2: scheme 2.

D11 discloses on pages 34 and 35 the procedure for crystallization induced asymmetric transformation whereby in the scheme on page 35 the process is exemplified for one particular compound.

The disclosure of D11 is thus novelty destroying for all claims 1 to 10.

The subject matter of present claims 1 to 10 is thus not novel over the disclosure of D1, D2 and in particular D11 (PCT Article 33.2).

1.2 D3 to D10 disclose compounds falling within the scope of present formulae (II) and (IIa) of present claims 11 and 12 (reference is made to the passages cited in the search report).

The subject matter of present claims 11 and 12 is thus not novel over the disclosure of D3 to D10 (PCT Article 33.2).

- 2. Inventive step
- 2.1 In addition to the novelty objection raised against present claims 1 to 10 and objection of lack of inventive step is raised:

It is said on page 1 of the description that the process disclosed in D2 is "unsuccessfully applied to other benzodiazepine derivatives". It is thus evident for the skilled person that the claimed process will certainly depend on the specific structure of the benzodiazepine to be prepared and in particular on the educt of formula (II)/(IIa).

In the present case examples 1 to 9 demonstrate the claimed process. However, the structure of the educts and products of these examples is very restricted compared with the claimed scope: the protecting group R2 is in each case CH3-O-phenyl-CH2-and "--XR4" represents either -NH2 or the group as given in example 9.

Such a restricted formula cannot be regarded as being representative for all possible structures falling within the scope of the formulae (I), (II), and (IIa). It is evident for the skilled person that these examples only show a process where in particular R_2 represents a -CH2-phenyl-O-CH3-group. A generalization to other structures cannot be accepted in the absence of any further data.

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The subject matter of present claims 1 to 10 and 11 to 12 insofar as novelty is given is thus not based on an inventive step (PCT Article 33.3).

3. The term "amino protecting group" has to be defined according to the definition given on page 6, lines 5 to 26(PCT Article 6).